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2,6-Dicyano-4-pyrone as a Novel and Multifarious Building Block for the Synthesis of 2,6-Bis(hetaryl)-4-pyrones and 2,6-Bis(hetaryl)-4-pyridinols

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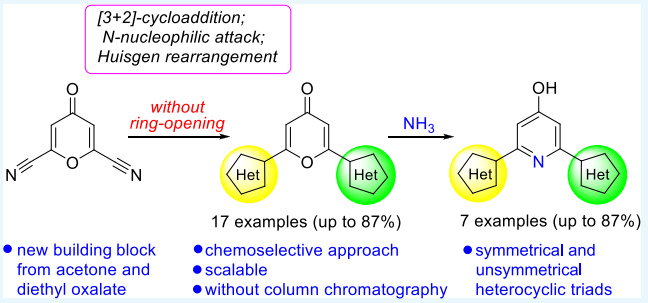
ABSTRACT: In this work, a three-stage and easily scalable synthesis of 2,6-dicyano-4-pyrone (overall yield of 45%) as a new convenient building block has been developed from diethyl acetonedioxalate. It was shown that the transformation with hydroxylamine and [3 + 2]-cycloaddition, in contrast to the reactions with hydrazines, selectively proceed through the attack at the cyano groups without the pyrone ring-opening to give symmetrical and unsymmetrical pyrone-bearing heterocyclic triads containing 1,2,4- and 1,3,4-oxadiazoles as well as tetrazole moieties. The reaction of 2,6-bis(hetaryl)-4-pyrones with ammonia afforded 2,6-bis(hetaryl)pyridines in 63−87% yields. The 4-pyridone/4-pyridinol tautomerism of 2,6-bis(hetaryl)pyridinols and the influence of the nature of adjacent azolyl moieties on this equilibrium have been discussed.



INTRODUCTION

2,6-Bis(azolyl)pyridines are an important class of heterocyclic triads that are attracting much attention as multidentate ligands and have found numerous applications due to their ability to form coordination compounds with various metal cations (Figure 1).[1] These complexes based on 2,6-bis(azolyl)-pyridines are actively used as luminescent materials,[2] as dyes in dye-sensitized solar cells (DSSC),[3] for the design of supramolecular assemblies and long-range ordered nanostructures,[4] for the separation of lanthanides and actinides,[5] magnetic materials,[6] and in a variety of catalytic systems.[7] For example, 2,6-bis(trifluoromethyltriazolyl)ligands and 2,6-bis(tetrazolyl)-pyridine are used in platinum coordination compounds for supramolecular nanostructures,[4a−e] which have potential application in optoelectronics, sensing, and biomedical fields,[4g] as an auxiliary ligand in ruthenium complexes in sensitizers for DSSC;[3] 2,6-bis(tetrazolyl)pyridine was also applied for the separation of actinides(III) (Am^{3+} and Eu^{3+}) from lanthanides-(III) (Figure 1).[5c]

In addition, heterocyclic assemblies based on 2,6-bis(1,2,4-oxadiazolyl)pyridines are of interest for designing biologically active structures as a G-quadracomplex ligand for interaction with nucleic acids (Figure 1).[8d,e] Pyridines bearing isomeric oxadiazolyl rings, 2,6-bis(1,3,4-oxadiazolyl)pyridines, were applied as electron-transporting materials for organic light-emitting diodes.[9] Much attention is paid to symmetrical triads[1] because of not only a structure−property relationship to design new materials but also the convenience of approaches for their synthesis. In recent years, unsymmetrical heterocyclic assemblies are intensively studied as promising ligands.[1a,c,d] For example, the ligand bearing the tetrazolyl and pyrazole moieties is actively used to obtain charge-neutral coordination compounds for magnetic materials[6] and fluorophores,[2e] and 2-benzimidazolyl-6-(pyrazolyl)pyridine is applied as a ligand in an effective catalyst for ethylene polymerization,[7e] β-alkylation of secondary alcohols,[7c] and transfer hydrogenation of ketones.[7d] At the same time, the construction of unsymmetrical 2,6-bis(hetaryl)pyridine structures is a rather difficult task due to multistage syntheses, which are usually based on various building blocks, and drawbacks connected with the selectivity of the reactions.

In the literature, the general method for the synthesis of 2,6-bis(hetaryl)pyridines involves the modification of the pyridine ring via transformations of pendent substituents (CO_2H, CN, COMe, ethynyl, and Hal).[1−9] Another approach is *de novo* synthesis of the pyridine ring from acyclic precursors or their heterocyclic synthetic equivalents. This approach makes it possible to introduce substituents into the pyridine ring without the use of multistep modifications of the pyridine fragment. Although this strategy is an important direction for modern organic synthesis due to effectivity and from the point

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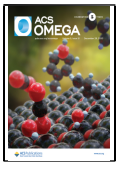

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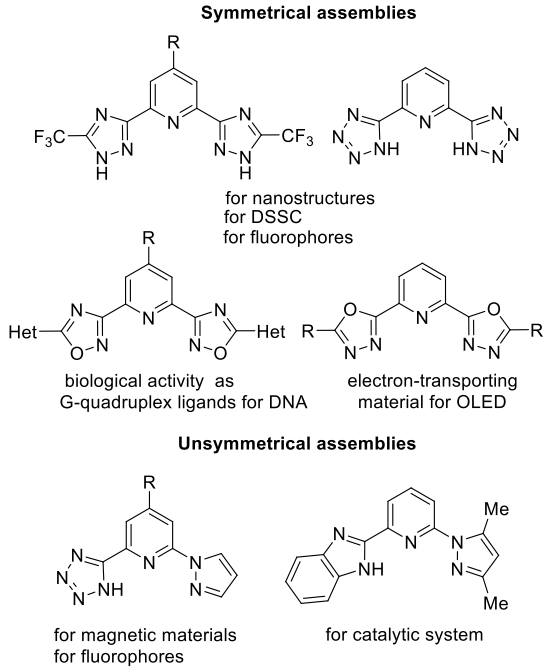
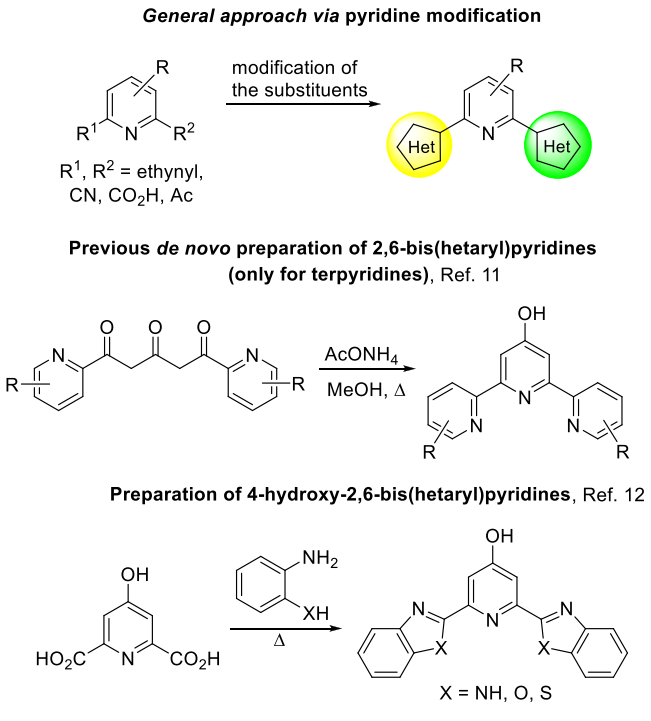


Figure 1. Some representative examples of 2,6-bis(hetaryl)pyridines.

of view of sustainable chemistry,[10] this protocol has not previously been described for 2,6-bis(azolyl)pyridines. To the best of our knowledge, there is only a method for the preparation of similar heterocyclic triads, 4-hydroxyterpyridines, based on cyclization of 1,5-bis(pyridyl)-substituted 1,3,5-triketones (Scheme 1).[11] Therefore, despite the importance and widespread application of 2,6-bis(hetaryl)-pyridines, there is a need for the development of novel and simple methods for the direct construction of new pyridine

Scheme 1. Main Strategies for the Synthesis of 2,6-Bis(hetaryl)pyridines

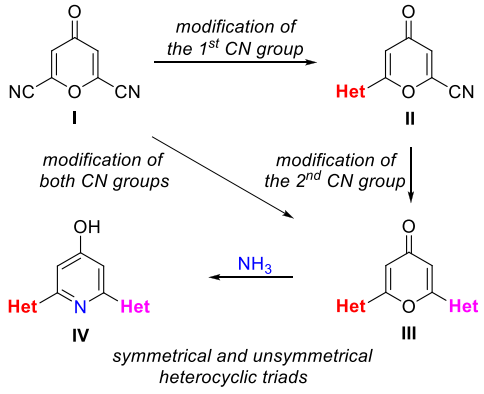


triads as well as the search of convenient, easily accessible building blocks for their preparations.

One of the important methods for the functionalization of 2,6-bis(hetaryl)pyridines is the incorporation of the hydroxyl group at the C-4 position.[12] On the one hand, these substances are attracting attention due to the possibility of the further functionalization of the hydroxyl group using the esterification reaction for the synthesis of alkoxy derivatives to increase the solubility in various solvents, or substitution with a halogen for incorporation into various structures.[12] On the other hand, the OH group allows the construction of coordination structures as a result of intermolecular hydrogen bonding.[13] One of the approaches for the synthesis of 2,6-bis(hetaryl)-4-hydroxypyridines is based on the reaction of chelidamic acid with *o*-phenylendiamines, *o*-aminophenol, and *o*-aminothiophenol under heating (Scheme 1).[5b,12a,c]

In this regard, it was interesting to consider a rare class of compounds, 2,6-bis(hetaryl)-4-pyrones, which are structurally similar to 2,6-bis(hetaryl)-4-hydroxypyridines and can be suggested as intermediates for the preparation of the latter. To find a general method for the synthesis of the pyrone triads, we assumed that these compounds can be considered as derivatives of natural and readily accessible chelidonic acid obtained by isosteric substitution of carboxyl groups by heterocyclic moieties.[14] Therefore, chelidonic acid or its simple derivatives can be starting structures for the construction of pyrone and pyridine triads. To our surprise, its closest and simplest derivative, dinitrile of chelidonic acid or 2,6-dicyano-4-pyrone (**I**, Scheme 2), has not been previously

Scheme 2. General Synthetic Strategy of This Work



described. Due to the presence of two activated cyano groups, this compound should undergo transformations with a wide range of nucleophilic reagents[15] as well as 1,3-dipolar cycloaddition reactions,[16] which, in turn, can be used to design various ligands. Although reactions can proceed *via* the attack at the cyano groups or the pyrone ring,[17] we were primarily interested in chemoselective reactions of the first type because it could lead to the formation of previously unknown heterocyclic triads based on 4-pyrone. On the other hand, we kept in mind that 2,6-dicyanopyridine is an extremely useful building block for the synthesis of a wide range of predominantly symmetrical 2,6-bis(azolyl)pyridine ligands,[2b,c,3,4a−e,5a,8c,d] and this strategy additionally motivated us to expand the range of such polycyclic structures.

2,6-Dicyano-4-pyrone (**I**) provides several possibilities for the construction of heterocyclic assemblies. The first path involves the modification of one cyano group, which opens

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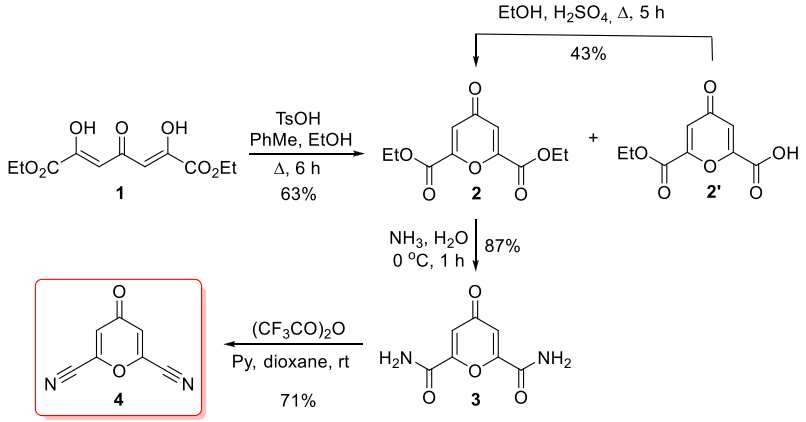
Scheme 3. Synthesis of 2,6-Dicyano-4-pyrone (4)



access to 6-hetaryl-2-cyano-4-pyrones (**II**). Subsequent reactions at the second cyano group should give unsymmetrical 2,6-bis(hetaryl)-4-pyrones **III**. Although 2,6-dicyano-4-pyrone (**I**) is a symmetrical molecule bearing the equivalent cyano groups, the activity of the cyano groups in compounds **I** and **II** can be very different, which will make it possible to implement this strategy.

Another approach is based on the one-stage modification of two cyano groups, which opens access to symmetrical pyrone triads **III**. There are few data on the synthesis of hetarylpyrones, including modification of the cyano group, but all of them include the narrow scope of compounds.[18,19] It should be noted that even cross-coupling reactions have limited application,[18a,b] for the preparation of hetarylpyrones because of the ring-opening processes.[18c,d] The subsequent selective reaction of 4-pyrones **III** with ammonia should open access to 2,6-bis(hetaryl)-4-hydroxypyridines **IV** *via* the pyrone ring-opening/ring-closure process.[19]

In this article, we describe a new, highly reactive, and simplest building block, 2,6-dicyano-4-pyrone, its preparation based on acetone and diethyl oxalate, the study of its reactivity toward *N*-nucleophiles (NH_2OH and hydrazines) and 1,3-dipoles (hydrazoic acid and nitrile oxides) for selective modifications of the CN groups, and application for the synthesis of heterocyclic pyrone and pyridine triads, which can be considered as promising ligands.

RESULTS AND DISCUSSION

At the first stage, we had to develop a convenient and easily scalable method for the synthesis of diethyl chelidonate **2** from the commercially available diethyl acetonedioxalate (**1**) (Scheme 3), which, in turn, can be obtained based on the well-known Claisen condensation of diethyl oxalate and acetone in the presence of sodium ethoxide.[20] In the literature, we were able to find two methods for the synthesis of diethyl ester **2**,[21,22] including a two-stage approach through the formation of chelidonic acid, which is further esterified by refluxing in EtOH saturated with HCl, or direct acid-catalyzed cyclization of ester **1**. The first method gave diethyl chelidonate (**2**) from chelidonic acid in only ∼25% yield[21] because of ineffective esterification of both CO_2H groups. Therefore, it is necessary to reflux the obtained mixture of chelidonic acid and monoethyl chelidonate in EtOH saturated with HCl several times to achieve an acceptable yield of ester **2**. This approach is feasible but extremely inconvenient for scaling due to low time−cost, low efficiency, using a lot of ethanol, and the additional stage for obtaining chelidonic acid. The second method is more attractive for the preparation of ester **2** because only one stage is required without unnecessary stages of hydrolysis of the CO_2Et group/subsequent esterification, but side processes can occur as a result of triketone cyclization.

Although the second method has been described in the literature,[22] in our hands, it has given unsatisfactory results. Therefore, optimization of the cyclization was carried out (see the Supporting Information), and it was found that the most favorable conditions are refluxing in toluene with *p*-toluenesulfonic acid (5 mass % relative to triketone **1**) with addition of EtOH to increase the solubility of the starting triketone **1**. Our procedure made it possible to obtain diethyl ester **2** in 63% yield and was easily scalable (up to 30 g). A byproduct of this reaction, monoethyl chelidonate (**2′**), was isolated in 37% yield and could be further used for the synthesis of ester **2** (43% yield).

Next, diethyl chelidonate (**2**) was treated with 20% aqueous ammonia solution for 1 h at 0 °C to give chelidonic acid diamide (**3**) in 87% yield (Scheme 3). An important feature of the reaction is the low temperature and its heterophase character, which determines the low reaction rate of the pyrone ring-opening with ammonia and the high selectivity of the CO_2Et group ammonolysis. Then, the resultant diamide **3** underwent dehydration in the presence of trifluoroacetic anhydride and pyridine in absolute dioxane, leading to the desired dinitrile **4** in 71% yield (the reaction was scaled up to 10 g) (Scheme 3).

We began to study the reactions of 2,6-dicyano-4-pyrone (**4**) with hydrazines in order to carry out the synthesis of pyrones bearing the amidrazone moiety. To our regret, we found that the transformation of pyrone **4** with hydrazine and phenylhydrazine proceeded *via* pyrone ring-opening and cyano group substitution to give pyrazolylacetic acid hydrazides **5a** and **5b** (26−55%) (Scheme 4). The formation of such products can be explained by the formation of acyl cyanide **A** as an intermediate, which is obtained as a result of the attack of a hydrazine molecule at the pyrone C-2 position.

It was found that the transformation of 2,6-dicyano-4-pyrone (**4**) with phenylhydrazine at room temperature led to the formation of many unidentified products. When the reaction mixture was maintained at −20 °C for 30 days, the yield of product **5b** was achieved to 55%. The structure of pyrazole **5b**

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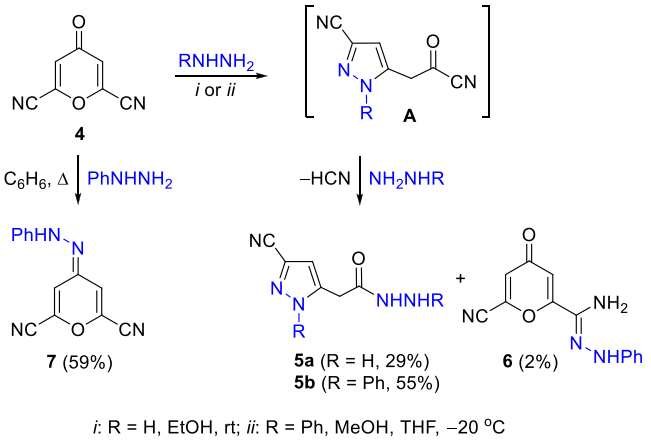
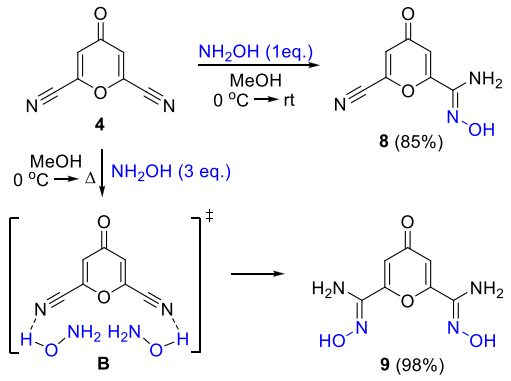
Scheme 4. Reactions of Dicyanopyrone 4 with Hydrazines



was confirmed by ^{13}C NMR spectroscopy, including a 2D $^{1}H-^{13}C$ HMBC experiment, and by comparison with the literature data for carbon chemical shifts in 2,3-disubstituted pyrazoles.[23] The desired amidrazone **6** was isolated in only trace amounts (2%) as a byproduct, and all our attempts to improve the yield of the target product were unsuccessful. When the reaction of dicyanopyrone **4** with phenylhydrazine was carried out in benzene, the direction of the attack strongly changed, and it proceeded at the C-4 atom to obtain phenylhydrazone **7** (59%).

The reaction of 2,6-dicyano-4-pyrone (**4**) with hydroxylamine, in accordance with the literature data, can lead to the formation of a product *via* the attack at the pyrone ring[24] or the cyano groups.[17b,19b] However, only amidoxime **8** and bis-amidoxime **9** were isolated as the products with 1 mol and 2 mol of hydroxylamine in 85% and 98% yields, respectively (Scheme 5). This selectivity can be explained by the fact that

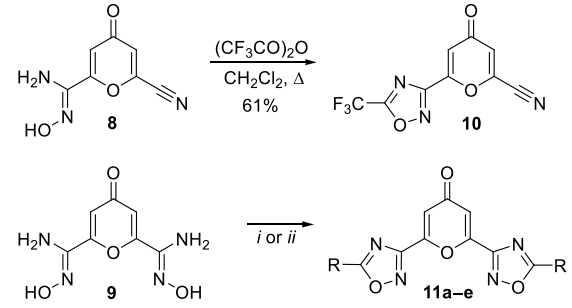
Scheme 5. Reactions of Dicyanopyrone 4 with Hydroxylamine



the reaction proceeds through intermediate **B**, where the proton of the OH group of hydroxylamine is coordinated with the nitrogen of the cyano group and promotes the attack of the amino group at the cyano group (Scheme 5). It is important to note that the reactivity of the cyano group of amidoxime **8** is significantly lower than that of 2,6-dicyano-4-pyrone (**4**) due to much lower solubility of **8** in MeOH, which determines chemoselectivity of the synthesis of compound **8**.

Obtained amidoximes **8** and **9** open access to both symmetrical and unsymmetrical 2,6-bis(1,2,4-oxadiazol-3-yl)-4-pyrones *via* the acylation reaction. Acylation of amidoxime **8** with trifluoroacetic anhydride in the presence of pyridine led to the formation of 6-oxadiazolyl-2-cyano-4-pyrone **10** in 61% yield (Scheme 6). This type of transformation under the action of benzoyl chloride or Ac_2O did not give the desired products.

Scheme 6. Acylation of Amidoximes 8 and 9 for the Preparation of Hetarylpyrones



Acylation of bis-amidoxime **9** proceeded smoothly to give symmetrical 2,6-bis(1,2,4-oxadiazol-3-yl)-4-pyrones **11a–11e** (Scheme 6). Bis-amidoxime **9** reacted with acetyl chloride in the presence of pyridine at 120 °C to form compound **11a** in 24% yield. The use of more reactive trifluoroacetic anhydride in dichloroethane upon reflux led to bis-adduct **11b** in 71% yield. When pyrone **9** was heated with PhCOCl at 120 °C for 18 h, pentacyclic compound **11c** was obtained in 46% yield. In this reaction, heterocyclic acyl chlorides of 2-furoic and nicotinic acids gave compounds **11d** and **11e**, bearing five heterocyclic rings in 33% and 63% yields, respectively.

The pyrone ring as an electron-withdrawing heterocyclic system decreases the nucleophilic properties of the amidoxime group, and as a result, the acylation reactions of **9** were carried out under prolonged heating. Acyl chlorides bearing electron-withdrawing R groups gave the products in the higher yields than acylation reagents bearing electron-donating R groups. This can be associated with both acylation and subsequent cyclization during formation of the 1,2,4-oxadiazole fragment.

Next, we studied the reactions of 1,3-dipolar cycloaddition of dinitrile **4** with 1,3-dipoles, which allow the one-step construction of heterocycles based on the cyano groups. The electron-withdrawing nature of **4** should facilitate these reactions because pyrone **4** can be considered as a hidden acyl cyanide, which is reactive in [3 + 2]-cycloaddition reactions.[16b] In addition, such transformations are usually promoted by acid catalysts, which can increase the selectivity of the interaction with the cyano groups due to the additional possibility of coordination with them.[16]

Although it is known that cycloaddition reactions of pyrones and their benzoannulated analogs with NaN_3 often occur as an attack at the pyrone ring to form triazoles,[25] we have found that the reaction of dinitrile **4** with an excess of NaN_3 (3 equiv) proceeded upon refluxing in aqueous THF in the presence of ammonium chloride as a catalyst selectively at the cyano groups to form 2,6-bis(tetrazolyl)-4-pyrone (**13**) in 87% yield. The selectivity of the reaction can be explained by coordination of the cyano group of pyrone **4** with the proton of hydrazoic acid (transition state **C**), as in the case of

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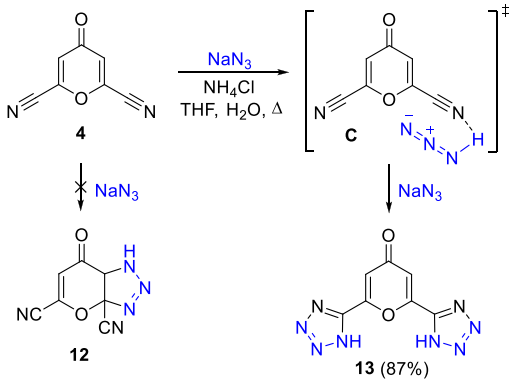
hydroxylamine (Scheme 7). Our attempts to carry out the cycloaddition at only one cyano group were unsuccessful

Scheme 7. Cycloaddition of Dicyanopyrone 4 with NaN_3



because this reaction did not proceed at room temperature. When dicyanopyrone **4** was heated with 1 equiv of NaN_3, bistetrazole **13** formed in a lower yield (13%).

Opposite to the azide, the BF_3-catalyzed reaction of dicyanopyrone **4** with benzonitrile oxides **D**, which were obtained by treating imidoyl chlorides **14** with triethylamine, led to 6-(1,2,4-oxadiazol-5-yl)-2-cyano-4-pyrones **15a**–**15c** in 29–65% yields as a result of the attack at only one cyano group. In this case, bis-addition product **16** was not detected even when 2.2 equiv of the corresponding 1,3-dipole was used. This fact indicates strong differences in the reactivity of the cyano groups in pyrones **4** and **15** (Scheme 8 and Table 1),

Scheme 8. Cycloaddition of Dicyanopyrone 4 with Nitrile Oxides

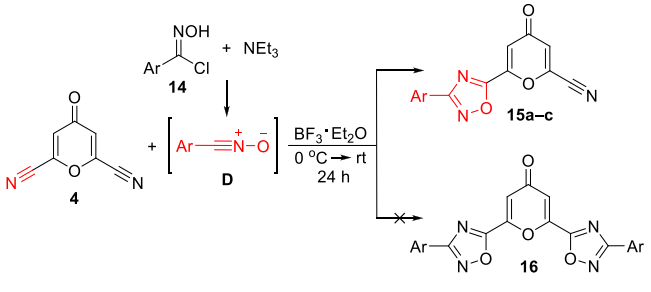


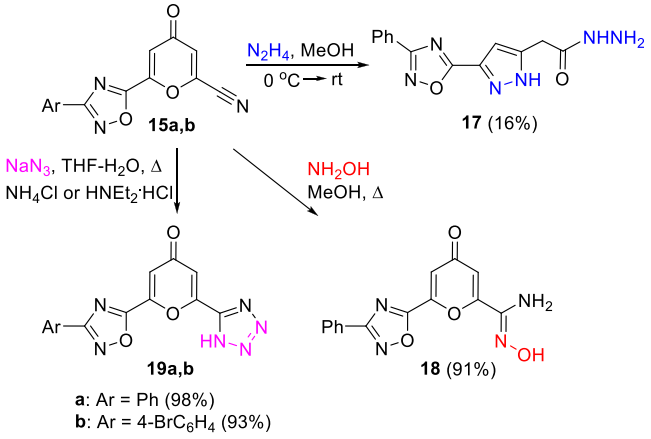
Table 1. Scope of the Cycloaddition of 2,6-Dicyano-4-pyrone (4) with Nitrile Oxides

Ar	product **15**	yields, %
Ph	**a**	65
4-BrC_6H_4	**b**	63
4-$MeOC_6H_4$	**c**	29
4-$NO_2C_6H_4$	**d**	traces

which makes it possible to stop the reaction at the stage of mono-adducts. When phenyl- and 4-bromophenyl-substituted nitrile oxides were used, the reaction proceeded in the higher yields. The introduction of the strong electron-donating group (*p*-MeO) into the aromatic ring of benzonitrile oxide led to a significant decrease in the product outcome. In the case of *p*-NO_2-substituted benzonitrile oxide, the product was detected only in trace amounts.

Since pyrones **15** bear the cyano group, its further modification allows the construction of asymmetrically substituted bis-hetaryl derivatives of 4-pyrones. The reaction of **15a** with hydrazine was followed by the pyrone ring-opening with the substitution of the cyano group and the formation of pyrazole **17** in a low yield (16%) (Scheme 9). When

Scheme 9. Some Chemical Properties of Cyanopyrones 15

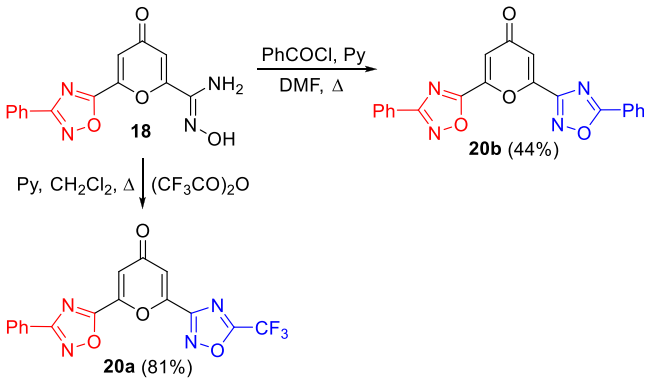


cyanopyrone **15a** was refluxed with hydroxylamine for 2 h in MeOH, amidoxime **18** was obtained selectively as the result of the attack at the cyano group in high yield (91%). Pyrone **15a** reacted with NaN_3 in aqueous THF in the presence of NH_4Cl as a catalyst to form tetrazole **19a** in 98% yield. It should be noted that the introduction of bromine at the C-4 position of the phenyl ring lowers the reactivity of the cyano group, and product **19b** was not obtained even upon refluxing for 10 h (TLC control). However, the use of diethylammonium chloride made it possible to isolate tetrazole **19b** in 93% yield upon reflux for 12 h (Scheme 9).

Subsequent treatment of amidoxime **18** with trifluoroacetic anhydride in the presence of pyridine in CH_2Cl_2 led to CF_3-containing pyrone **20a** in 81% yield. When benzoyl chloride was used as an acylating reagent at 120 °C in DMF, 2,6-bis(1,2,4-oxadiazolyl)pyrone **20b** bearing two regioisomeric phenyl-substituted 1,2,4-oxadiazole rings was prepared (Scheme 10).

Having in our hands tetrazolyl-substituted pyrones **19**, we decided to expand the range of asymmetrical assemblies of 4-pyrone using the Huisgen rearrangement (Scheme 11). It was

Scheme 10. Acylation of Amidoxime 18 for the Construction of 2,6-Bis(1,2,4-oxadiazolyl)pyrones 20



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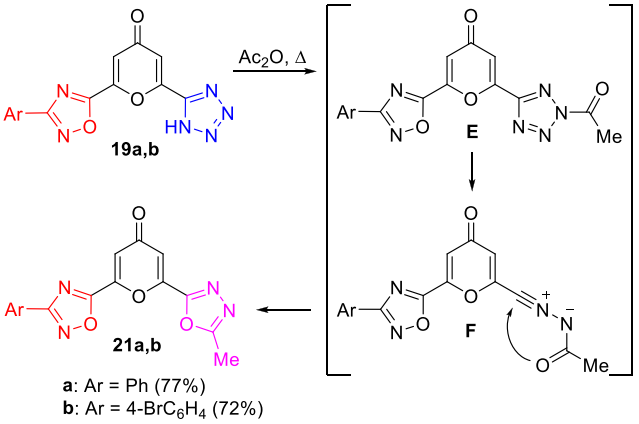
Scheme 11. Synthesis of Unsymmetrical 2,6-Bis(hetaryl)-4-pyrones 21 *via* the Huisgen Rearrangement of Tetrazolylpyrones 19



found that tetrazoles **19** react with acetic anhydride under heating without any catalyst to form 1,3,4-oxadiazolyl-substituted heterocyclic systems **21**. A plausible reaction mechanism includes intermediates **E** and **F**, and unsymmetrical compounds **21a** and **21b** formed selectively as the only products. Our attempts to use other acylating reagents were unsuccessful and did not allow to isolate any products in pure form.

Another task was to involve 2,6-bis(tetrazolyl)-4-pyrone (**13**) in the Huisgen rearrangement to obtain symmetrical 2,6-bis(1,3,4-oxadiazolyl)-4-pyrones **22** (Scheme 12 and Table 2).

Scheme 12. Synthesis of 2,6-Bis(1,3,4-oxadiazol-2-yl)-4-pyrones 22 *via* the Huisgen Rearrangement of 2,6-Bis(tetrazolyl)-4-pyrone (13)

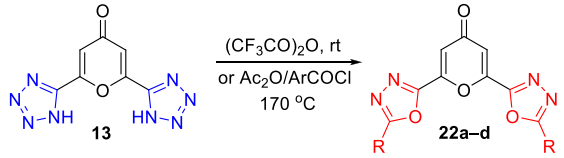


Table 2. Scope of Symmetrical 2,6-Bis(hetaryl)-4-pyrones 22 Prepared *via* Huisgen Rearrangement of Bis(tetrazolyl)pyrone 13

R	product **22**	yields
Me	**a**	92
CF_3	**b**	44
Ph	**c**	77
2-furyl	**d**	44

When pyrone **13** was refluxed in acetic anhydride for ~48 h (until complete dissolution), bis(1,3,4-oxadiazolyl)-4-pyrone **22a** was obtained in 92% yield and its structure was confirmed by X-ray diffraction analysis. Compound **22a** exists in a solid state as a planar *anti*-conformer that can be explained by electrostatic interaction of 1,3,4-oxadiazole rings (Figure 2). An important feature of the reaction was the usage of a large excess of acetic anhydride (for 0.1 g of **13**−10 mL of Ac_2O) because a decrease in the amount of the acylating reagent (by three to four times) did not allow achieving good conversion. Trifluoroacetic anhydride is more reactive than Ac_2O, and the Huisgen rearrangement proceeded at room temperature for 10

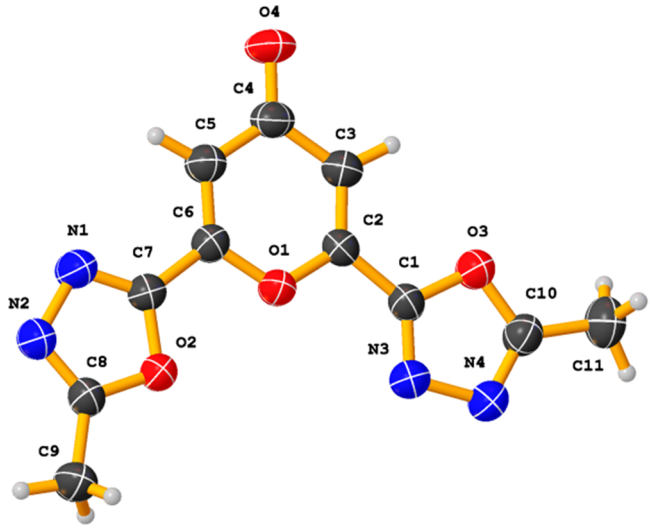
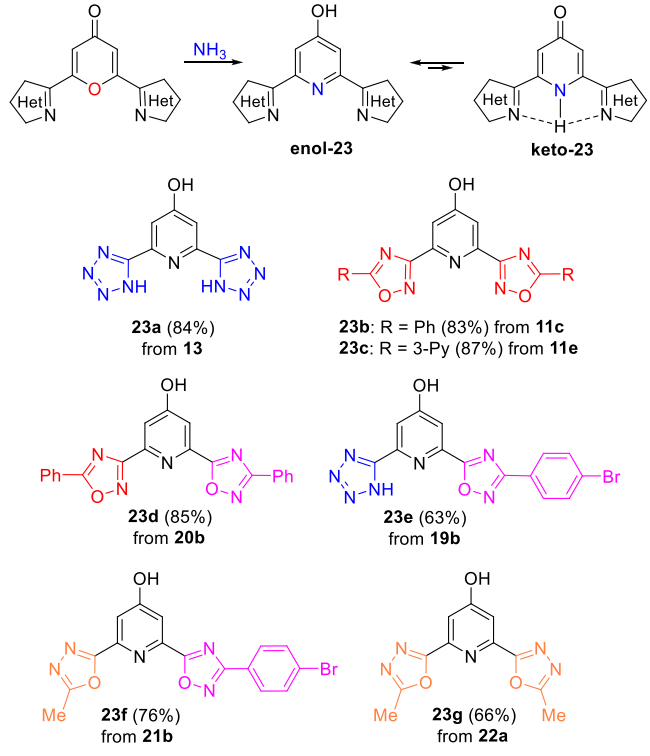


Figure 2. Molecular structure of 2,6-bis(1,3,4-oxadiazolyl)-4-pyrone **22a** with atoms represented by thermal vibration ellipsoids of 50% probability.

days (until complete dissolution) to form the desired product **22b**, albeit in a lower yield (44%). For the synthesis of pentacyclic systems, the reaction of pyrone **13** with aroyl chlorides was carried out at 170 °C for 8 h without any solvents and catalysts. As a result, compounds **22c** and **22d** were obtained in 77% and 44% yields, respectively.

Next, the prepared 2,6-bis(hetaryl)-4-pyrones were treated with ammonia to obtain 2,6-bis(hetaryl)-4-pyridines (Table 3). It is known that oxadiazole rings[26] can undergo ring-opening transformation with ammonia, and therefore, it was interesting

Table 3. Synthesis of 2,6-Bis(hetaryl)pyridines 23 from Pyrones



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to determine the chemoselectivity of the process. 4-Pyridines **23** were obtained in 63−87% yields, and the outcome of the transformation is influenced by both the nature of the adjacent heterocycles and solubility of the starting 4-pyrones. It should be noted that the reaction proceeded exclusively at the pyrone ring, and the tricyclic products of the ammonia attack on other heterocyclic rings were not isolated. The reaction of 2,6-bis(tetrazolyl)-4-pyrone **13** with aqueous ammonia (25%) proceeded for 2 days at room temperature due to its ability to form an ammonium salt, which is soluble in water. After further treatment with hydrochloric acid, 2,6-bis(tetrazolyl)-4-hydroxypyridine (**23a**) was prepared in 84% yield.

2,6-Bis(hetaryl)-4-pyrones bearing 1,2,4-oxadiazole, 1,3,4-oxadiazole, and tetrazole substituents reacted with an ethanolic ammonia solution (12−15%) under harsher conditions upon heating at 100 °C in an autoclave. It should be noted that trifluoromethylated bis(1,2,4-oxadiazolyl)-4-pyrone **11b** did not follow by the pyrone ring-opening under the same conditions, but the reaction gave bis-amidoxime **9** as a product of detrifluoroacetylation during an ammonia attack on the 1,2,4-oxadiazole ring activating by the CF_3 group. The pyridones **23b−23g** could form salts with ammonia and were additionally dried at 120 °C to remove NH_3. These salts were observed in the ^{1}H NMR spectra by the up-field shift of the signals of the pyridine protons and could be isolated in pure form (for compound **23c**).

The pyridone−pyridinol type of tautomerism is of considerable interest because it can influence biological activity[27a] and coordination properties,[27b] and at the same time, it is rather limitedly studied. It is known that the prototropic tautomerism can be influenced by many factors, such as the nature of substituents in the pyridine ring, temperature, the ability to form intermolecular and intramolecular hydrogen bonds, and the polarity of the solvent.[28] It has also been shown[28a] that 4-hydroxyterpyridines, which are similar to pyridines **23**, can undergo easy interconversion of 4-pyridone and 4-pyridinol tautomers in solution, in the gas phase, and in the crystalline state, where more favorable forms are different.

Pyridines **23** can exist in keto-**23** or enol-**23** tautomeric forms (Table 3). Pendant heterocyclic substituents are able to participate in the formation of intra- or intermolecular hydrogen bonds determining the structure of the pyridine ring and, therefore, influence on pyridinol−pyridone tautomerism. On the one hand, the pyridone form (keto-**23**) is known to be more favorable[28] and can be additionally stabilized *via* intramolecular hydrogen bonding between the NH group of the pyridone ring and the C═N group of oxadiazolyl or tetrazolyl moieties. On the other hand, in our case, the population of the less favorable hydroxy form enol-**23** can be increased through (1) inter- and intramolecular hydrogen bonding of the hydroxy hydrogen with an H-bond acceptor (the azolyl moiety),[28a] (2) intramolecular interaction of the pyridine nitrogen with an H-bond donor (the tetrazole moiety), or (3) the presence of the electron-withdrawing azolyl groups, which lead to a relative decrease in the basic properties of the pyridine nitrogen atom.

In the ^{1}H and ^{13}C NMR spectra in DMSO-d_6, these compounds possess one set of signals, which indicates the existence of one tautomer. Pyridine protons H-3 and H-5 of compounds **23** were observed at δ 7.36−7.77 ppm and were downfield shifted compared to the same protons of the corresponding pyrones by $\Delta\delta$ ($\delta_{pyridine} - \delta_{pyrone}$) = 0.20−0.65 ppm. This magnitude can be connected with the existence of substances in the pyridinol (enol-**23**) form because of higher aromaticity of the pyridinol ring than the pyridone ring.[27a] In the case of pyridine **23a**, which bears two tetrazole rings, the greatest difference in chemical shifts ($\Delta\delta$ = 0.65 ppm) can be connected with the intramolecular hydrogen bonds of pyridine nitrogen with the protons of the tetrazole rings, which leads to the stabilization of the pyridinol form and *syn*-conformation. Additionally, the carbon C-4 of the pyridine ring was detected in the ^{13}C NMR spectra for symmetrical compounds **23a−23c** and **23g** at δ 166.5−171.5 ppm and for compounds **23e** at δ 165.4 ppm, which unambiguously indicates the existence of these compounds in the pyridinol form. The assignment of the carbonyl groups was based on the ^{1}H−^{13}C HMBC experiment (for **23e**) and the integral intensities of the signals (for **23a−23c** and **23g**). An additional confirmation of the proposed structure is the detected downfield signal of the OH proton for compound **23c** at 11.16 ppm, though, in other cases, the signal of the OH proton was not observed because of broadening.

For solid-state FTIR spectra of pyridines **23a**, **23c**, and **23e−23f**, the C═O and NH stretches were absent, and a broad absorbance band at 2000−3400 cm^{-1} can be attributed to the OH stretch because of the OH···N═(azole) intermolecular hydrogen bonding.[28a] These spectral data indicate that compounds **23a**, **23c**, and **23e−23f** exist in a solid state only in 4-hydroxypyridine form, which is stabilized by the hydrogen bond. Although the solid-state FTIR spectra of **23b**, **23d**, and **23g** contain a broad absorbance band of the OH stretch of the pyridinol form, a middle intensive band of the C═O stretch at 1635−1662 cm^{-1} and a sharp band at 3368 cm^{-1} (for **23b**) were observed. The latter can be attributed to the stretch of the NH group, which participates in intramolecular hydrogen bonding with the C═N moiety of the azole. This result can be explained by the existence of substances **23b**, **23d**, and **23g** in solid in both 4-pyridone and 4-pyridinol forms as in the case of 4-hydroxyterpyridines.[28a]

CONCLUSIONS

In summary, a convenient and scalable method has been found for the synthesis of highly reactive 2,6-dicyano-4-pyrone from diethyl acetonedioxalate in three stages. It has been shown that this pyrone reacts chemoselectively with N-nucleophiles and 1,3-dipoles through pyrone ring-opening or an attack at one or two cyano groups. The directions of the transformations are mainly dependent on the nature of the reagents. Modifications of the cyano groups of 2,6-dicyano-4-pyrone have been developed as a general approach for the facile construction of 2,6-bis(hetaryl)-4-pyrones, which were used for the novel synthesis of 2,6-bis(hetaryl)-4-pyridines *via* the chemoselective ring-opening reaction with ammonia. Pyridine and pyrone triads bearing oxadiazole and tetrazole moieties are of further interest as promising novel ligands for the synthesis of coordination compounds. Obtained 2,6-bis(hetaryl)pyridines exist in solution as the predominant 4-hydroxypyridine tautomeric form.

EXPERIMENTAL SECTION

NMR spectra were recorded on a 400 MHz spectrometer (^{1}H, 400 MHz; ^{19}F, 376 MHz; ^{13}C, 101 MHz), 500 MHz spectrometer (^{1}H, 500 MHz; ^{19}F, 376 MHz; ^{13}C, 126 MHz), and 600 MHz spectrometer (^{1}H, 600 MHz; ^{13}C, 151 MHz) in DMSO-d_6 or $CDCl_3$. The chemical shifts (δ) are reported in

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ppm relative to the internal standard TMS (^{1}H NMR) and C_6F_6 (^{19}F NMR) and to residual signals of the solvents ($CHCl_3$ (δ 7.26, ^{1}H NMR) and DMSO-d_6 (δ 2.50, ^{1}H NMR)). The ^{1}H−^{13}C HMBC experiments were carried out on 400 MHz and 600 MHz spectrometers. IR spectra were recorded on a FTIR spectrometer with an ATR accessory. High-resolution mass spectra (HRMS) were recorded on an HRMS-ESI-QTOF instrument. Elemental analysis was performed on a Perkin Elmer PE 2400 automatic analyzer. All solvents were dried and distilled by standard procedures. Transformations with cyanopyrones as well as isolation of products of the reactions should be carried out in a hood and/or closed vessel because of formation and liberation of HCN.

Diethyl 4-Oxo-4*H*-pyran-2,6-dicarboxylate (2). *Method A.* Diethyl 2,4,6-trioxoheptanedioate (**1**) (30.00 g, 0.1162 mol) was added in a mixture of toluene (200 mL) and EtOH (95%, 50 mL) containing TsOH·H_2O (1.50 g, 0.0079 mol). The reaction mass was refluxed for 6 h. The precipitate was filtered off (1.57 g), the filtrate was evaporated, and toluene (100 mL) was added. The insoluble precipitate of monoethyl chelidonate (**2′**) (9.11 g, 37%) was filtered off, the filtrate was evaporated, and hexane was added. The precipitate was filtered off and dried. Yield 63% (17.56 g), yellow powder, mp 59−60 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42 (t, J = 7.1 Hz, 6H, 2Me), 4.46 (q, J = 7.1 Hz, 4H, $2CH_2$), 7.17 (s, 2H, H-3, H-5). The data are in accordance with the literature.[29]

Method B. Monoethyl chelidonate (**2′**) (1.00 g, 4.71 mmol) was refluxed in EtOH (15 mL) containing H_2SO_4 (1 mL) for 5 h. After that, the reaction mixture was cooled to room temperature and diluted with H_2O (10 mL), and the product was extracted with EtOAc (3 × 7 mL). The combined organic extracts were washed with H_2O (7 mL), brine (7 mL), dried with Na_2SO_4, and evaporated. The residue was diluted with hexane (10 mL), and the product was filtered. Yield 43% (0.50 g), yellow powder, mp 59−60 °C.

4-Oxo-4*H*-pyran-2,6-dicarboxamide (3). In a 1 L flask, carefully milled diethyl chelidonate (**2**) (20.00 g, 0.110 mol) was added to an aqueous solution of ammonia (20%, 200 mL) cooled in an ice bath. The resulting suspension was stirred for 1 h at 0 °C. The precipitate that formed was filtered through a thick filter paper (the precipitate is very fine and poorly filtered) and washed with H_2O (50 mL). Yield 87% (15.16 g), white powder, mp >350 °C. IR (ATR): 3366, 3184, 3059, 1698, 1636 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.88 (s, 2H, H-3, H-5), 8.21 (s, 2H, 2NHH), 8.65 (s, 2H, 2NHH); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 116.3, 156.0, 159.6, 178.6. Anal. Calcd for $C_7H_6N_2O_4$: C, 46.16; H, 3.32; N, 15.38. Found: C, 46.39; H, 3.57; N, 15.61.

2,6-Dicyano-4*H*-pyran-4-one (4). Trifluoroacetic anhydride (37.5 mL, 0.293 mol) was added to a mixture of finely ground chelidonic acid diamide (**3**) (10.00 g, 54.9 mmol) and pyridine (23.3 mL, 0.289 mol) in dry dioxane (40 mL) under stirring in an ice bath. After that, the suspension was stirred for 30 min at the same temperature and then 1 day at 20 °C. The reaction mixture was diluted with H_2O (300 mL), and the product was extracted with $CHCl_3$ (4 × 70 mL). The organic phase was evaporated, and the resulting dinitrile **4** was recrystallized from EtOH or toluene. The product was dried in air at room temperature. Yield 71% (3.20 g), yellow or gray crystals, mp 128−129 °C. IR (ATR): 2248, 1655, 1622, 1593, 1389 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.57 (s, 2H, H-3, H-5); ^{13}C (101 MHz, DMSO-d_6): δ 111.1 (CN), 125.7 (C-3, C-5), 138.3 (C-2, C-6), 175.1 (C═O). Anal. Calcd for $C_7H_2N_2O_2$: C, 57.54; H, 1.38; N, 19.17. Found: C, 57.23; H, 1.35; N, 19.06.

2-[3-(Cyano)pyrazol-5-yl]acetohydrazide (5a). Hydrazine hydrate (0.20 mL, 4.00 mmol) was added to a suspension of 2,6-dicyano-4*H*-pyran-4-one (**4**) (0.150 g, 1.03 mmol) in EtOH (3 mL), and the reaction mixture was stirred at ∼20 °C for 2.5 h. The precipitate was filtered off and recrystallized from EtOH. Yield 29% (50 mg), yellow crystals, mp 201−202 °C. IR (ATR): 3279, 3127, 3062, 2242, 1640, 1591, 1540 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.50 (s, 2H, NH_2), 4.28 (s, 2H, CH_2), 6.73 (s, 1H, CH Pz), 9.27 (br. s, 1H, CONHNH$_2$), 13.80 (br. s, 1H, NH Pz); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 30.3, 109.8, 115.0, 123.5, 139.1, 166.9. Anal. Calcd for $C_6H_7N_5O$: C, 43.63; H, 4.27; N, 42.41. Found: C, 43.75; H, 4.31; N, 42.35.

2-(3-Cyano-1-phenyl-1*H*-pyrazol-5-yl)-*N*′-phenylacetohydrazide (5b). A solution of phenylhydrazine (0.560 g, 5.18 mmol) in MeOH (3 mL) was cooled to −20 °C and added to a solution of 2,6-dicyano-4-pyrone (**4**) (0.250 g, 1.71 mmol) in dried THF (3 mL). The reaction mixture was kept for 30 days at −20 °C. On seventh day, the formation of a small amount of amidrazone 6-cyanocomanic acid (**6**) as solid was observed. After that, amidrazone **6** was filtered off, and the resulting filtrate was diluted with H_2O (13 mL) and concd HCl (2 mL). Over time, the resinous mass crystallized. The precipitate that formed was filtered off and recrystallized from toluene (∼16 mL) to separate the insoluble admixtures. Yield 0.300 g (55%), grayish powder, mp 170−171 °C. IR (ATR): 3364, 3271, 3052, 2242, 1701, 1598 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): *syn*-**5b** (83%): δ 3.79 (s, 2H, CH_2), 6.53 (d, J = 7.7 Hz, 2H, H-2, H-6 Ph), 6.69 (t, J = 7.2 Hz, 1H, H-4 Ph), 7.11 (s, 1H, H-4 Pz), 7.08 (t, J = 8.2 Hz, 2H, H-3, H-5 Ph), 7.56−7.63 (m, 5H, Ph), 7.71 (d, J = 2.4 Hz, 1H, PhNHNH), 9.81 (d, J = 2.4 Hz, 1H, PhNHNH); *anti*-**5b** (17%), selected signals: δ 3.79 (s, 2H, CH_2), 6.76 (t, J = 7.3 Hz, 1H, H-4, Ph), 7.06 (s, 1 H, H-4 Pz), 7.14 (t, J = 8.1 Hz, 2H, H-3, H-5 Ph), 7.43−7.47 (m, 2H, Ph), 7.51−7.55 (m, 3H, Ph), 7.92 (s, 1H, PhNHNH), 9.25 (s, 1H, PhNHNH); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 30.7 (CH_2), 112.0, 112.8 (C-4 Pz), 114.3, 118.5, 124.0, 125.5, 128.6, 129.47, 129.51, 138.0, 139.8 (C-5 Pz), 148.8 (C-3 Pz), 167.1 (C═O). Found: C, 68.23; H, 4.62; N, 22.24. Anal. Calcd for $C_{18}H_{15}N_5O$: C, 68.13; H, 4.76; N, 22.07.

(*Z*)-6-Cyano-4-oxo-*N*′-phenyl-4*H*-pyran-2-carbohydrazonamide (6). Yield 2% (0.010 g), red powder, mp 280−281 °C. IR (ATR): 3430, 3361, 3262, 1594 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.21 (s, 2H, NH_2), 6.74 (t, J = 7.3 Hz, 1H, H-4 Ph), 6.90 (d, J = 2.3 Hz, 1H, H-3 pyrone), 7.05 (d, J = 7.9, 2H, H-2, H-6 Ph), 7.21 (t, J = 7.8 Hz, 2H, H-3, H-5 Ph), 7.32 (d, J = 2.3 Hz, 1H, H-5 pyrone), 8.93 (s, 1H, NHPh); ^{13}C NMR (101 MHz, DMSO-d_6): δ 111.6, 111.9, 112.2, 118.8, 124.8, 128.9, 133.5, 136.7, 145.4, 159.2, 175.9. Found: C, 61.52; H, 4.12; N, 22.24. Anal. Calcd for $C_{18}H_{10}N_4O_2$: C, 61.41; H, 3.96; N, 22.04.

2,6-Dicyano-4*H*-pyran-4-one Phenylhydrazone (7). 2,6-Dicyano-4*H*-pyran-4-one (**4**) (0.100 g, 0.68 mmol) and phenylhydrazine (0.080 g, 0.74 mmol) were refluxed in benzene (1 mL) for 6 h. After cooling, the precipitate was filtered off. Yield 59% (0.096 g), red powder, mp 225−226 °C. IR(ATR) 3324, 2228, 1599 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.85 (t, J = 7.2 Hz, 1H, H-4 Ph), 7.10 (d, J = 7.9 Hz, 2H, H-2, H-6 Ph), 7.20 (d, 1H, J = 1.6 Hz, CH pyrone), 7.25 (t, J = 7.7 Hz, 2H, Ph), 7.62 (d, J = 1.6 Hz, 1H, CH

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pyrone), 10.10 (s, 1H, NH); $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO-d_6): δ 112.7, 112.8, 114.0, 120.5, 124.8, 125.5, 127.9, 128.4, 129.2, 144.0. Anal. Calcd for $C_{13}H_8N_4O$: C, 66.10; H, 3.41; N, 23.72. Found: C, 66.22; H, 3.61; N, 23.82.

(*Z*)-6-Cyano-*N*′-hydroxy-4-oxo-4*H*-pyran-2-carboximidamide (8). A solution of NH_2OH, which was obtained by stirring $NH_2OH{\cdot}HCl$ (0.265 g, 4.11 mmol) and KOH (0.200 g, 3.56 mmol) in MeOH (3 mL) for 5 min, was added dropwise to a suspension of 2,6-dicyano-4*H*-pyran-4-one (**4**) (0.500 g, 3.42 mmol) in MeOH (3 mL) under stirring in an ice bath. Then, the reaction mixture was stirred in an ice bath for 30 min and then 1 h at 20 °C. The precipitate that formed was filtered. Yield 85% (0.52 g), yellow powder, 290−295 °C (decomp.). IR (ATR): 3469, 3323, 3179, 1668, 1617, 1592, 1578, 1445, 1395 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.14 (s, 2H, NH_2), 6.79 (d, J = 2.4 Hz, 1H, H-3), 7.34 (d, J = 2.4 Hz, 1H, H-5), 10.63 (s, 1H, OH); $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6): δ 111.9, 113.2, 124.8, 137.4, 144.6, 158.2, 178.3. Anal. Calcd for $C_7H_5N_3O_3$: C, 46.93; H, 2.81; N, 23.46. Found: C, 46.94; H, 2.97; N, 23.60.

(2*Z*,6*Z*)-*N*′2,*N*′6-Dihydroxy-4-oxo-4*H*-pyran-2,6-bis(carboximidamide) (9). A solution of NH_2OH, which was obtained from $NH_2OH{\cdot}HCl$ (0.684 g, 10.6 mmol) and KOH (0.504 g, 8.98 mmol) in MeOH (3 mL) under stirring for 5 min, was added dropwise to a suspension of 2,6-dicyano-4*H*-pyran-4-one (**4**) (0.400 g, 2.74 mmol) in MeOH (3 mL) in an ice bath. Then, the reaction mixture was stirred at room temperature for 24 h and then was refluxed for 1 h. The precipitate that formed was filtered and washed with MeOH. Yield 98% (0.569 g), yellow powder, decomp. >400 °C. IR (ATR): 3367, 3067, 2845, 1626, 1568, 1578, 1417, 903 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.21 (s, 4H, $2NH_2$), 6.61 (s, 2H, H-3, H-5), 10.43 (s, 2H, 2OH); $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO-d_6): δ 111.6, 145.2, 157.1, 177.6. Anal. Calcd for $C_7H_8N_4O_4$: C, 39.63; H, 3.80; N, 26.41. Found: C, 39.71; H, 3.87; N, 26.37.

4-Oxo-6-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)-4*H*-pyran-2-carbonitrile (10). Trifluoroacetic anhydride (0.315 mL, 2.24 mmol) was gradually added to a mixture of amidoxime **8** (0.100 g, 0.558 mmol) and pyridine (0.177 g, 2.24 mmol) in dry CH_2Cl_2 (2 mL) at room temperature. The reaction mixture was stirred at the same temperature until amidoxime **8** was completely dissolved, and after that, the reaction mixture was refluxed for 1 h. The solvent was evaporated under reduced pressure, and H_2O (10 mL) was added to the residue. The precipitate that formed was filtered off and recrystallized from a mixture of petroleum ether−toluene. Yield 61% (0.087 g), white crystals, mp 134−135 °C. IR (ATR): 3094, 1660, 1426 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.27 (d, J = 2.4 Hz, 1H, H-5), 7.60 (d, J = 2.4 Hz, 1H, H-3); $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO-d_6): δ 111.6, 114.3 (q, $^{1}J_{C,F}$ = 273.5 Hz, CF_3), 118.5, 125.4, 138.0, 151.5, 162.7, 165.9 (q, $^{1}J_{C,F}$ = 44.6 Hz, C−CF_3), 175.8. Anal. Calcd for $C_9H_2F_3N_3O_3$: C, 42.04; H, 0.78; N, 16.34. Found: C, 42.34; H, 0.92; N, 16.60.

2,6-Bis(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)-4*H*-pyran-4-one (11b). Trifluoroacetic acid anhydride (0.500 g, 2.38 mmol) was added dropwise to a mixture of pyridine (0.188 g, 2.38 mmol) and bisamidoxime of chelidonic acid (**9**) (0.100 g, 0.471 mmol) in dry 1,2-dichloroethane (3 mL). The reaction mixture was stirred at room temperature for 30 min and then was refluxed for 6 h. After that, the solvent was evaporated under reduced pressure with H_2O, and the precipitate was filtered off and recrystallized from toluene−hexane (1:10). Yield 71% (0.121 g), white crystals, mp 166−167 °C. IR (ATR) 3070, 1664, 1637, 1301, 1153 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.30 (s, 2H, H-3, H-5); ^{19}F NMR (471 MHz, DMSO-d_6) δ 98.00 (s, 3F, CF_3); $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO-d_6): δ 114.4 (q, J = 273.6 Hz), 118.3, 151.1, 165.8 (q, J = 45.0 Hz), 176.4. Anal. Calcd for $C_{11}H_2F_6N_4O_4$: C, 35.89; H, 0.55; N, 15.22. Found: C, 35.85; H, 0.57; N, 15.39.

General Method for the Preparation of 2,6-Bis(1,2,4-oxadiazol-3-yl)-4*H*-pyran-4-ones (11a and 11c−11e). Acylchloride (2.348 mmol) was added dropwise to pyridine (0.190 g, 2.402 mmol) and bisamidoxime of chelidonic acid (**9**) (0.100 g, 0.471 mmol) in DMF (3 mL). The reaction mixture was stirred at room temperature for 30 min and was heated at 120 °C for 18 h (for **11a**, 6 h).

*2,6-Bis(5-methyl-1,2,4-oxadiazol-3-yl)-4H-pyran-4-one (**11a**).* The reaction mixture was cooled to room temperature and diluted with H_2O (10 mL). The aqueous layer was extracted with EtOAc (3 × 5 mL), and the combined organic extracts were washed with brine (3 mL), dried (Na_2SO_4), and evaporated. Yield 24% (0.029 g), yellow powder, mp 185−188 °C. IR (ATR): 3071, 1668, 1640, 1574, 1335, 881 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.73 (s, 6H, CH_3), 7.04 (s, 2H, H-3, H-5); $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO-d_6): δ 12.1, 116.9, 152.6, 162.3, 177.0, 178.9. Anal. Calcd for $C_{11}H_8N_4O_4$: C, 50.77; H, 3.10; N, 21.53. Found: C, 50.52; H, 2.93; N, 21.26.

*2,6-Bis(5-phenyl-1,2,4-oxadiazol-3-yl)-4H-pyran-4-one (**11c**).* The reaction mixture was cooled and diluted with H_2O (5 mL). The precipitate that formed was filtered off and recrystallized from toluene−hexane. Yield 46% (0.062 g), gray powder, mp 226−227 °C. IR (ATR) 3052, 1664, 1641, 1560, 1336, 1275, 750 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.24 (s, 2H, H-3, H-5), 7.72 (m, 6H, Ph), 8.23 (m, 4H, Ph); ^{13}C NMR (400 MHz, DMSO-d_6): δ 117.4, 122.6, 128.3, 129.8, 134.1, 152.7, 163.0, 176.4, 177.0. Anal. Calcd for $C_{21}H_{12}N_4O_4{\cdot}H_2O$: C, 62.69; H, 3.51; N, 13.92. Found: C, 62.42; H, 3.53; N, 13.87.

*2,6-Bis(5-(furan-2-yl)-1,2,4-oxadiazol-3-yl)-4H-pyran-4-one (**11d**).* The precipitate that formed was filtered off and recrystallized from toluene−hexane. Yield 33% (0.058 g), brown crystals, mp 263−264 °C. IR (ATR) 3143, 3103, 1667, 1630, 1330, 1289, 844 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.93 (dd, J = 3.6 Hz, J = 1.7 Hz, 1H, H-4 furan), 7.29 (s, 2H, H-3, H-5), 7.78 (dd, J = 3.6 Hz, J = 0.7 Hz, 2H, H-3 furan), 8.25 (dd, J = 1.7 Hz, J = 0.7 Hz, 2H, H-5 furan); $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6): δ 113.3, 117.4, 119.0, 138.3, 149.1, 152.4, 162.8, 168.1, 176.7. Anal. Calcd for $C_{17}H_8N_4O_6$: C, 56.05; H, 2.21; N, 15.38. Found: C, 55.94; H, 2.32; N, 15.15.

*2,6-Bis(5-(pyridin-3-yl)-1,2,4-oxadiazol-3-yl)-4H-pyran-4-one (**11e**).* The reaction was cooled to room temperature and diluted with H_2O (5 mL). The precipitate that formed was filtered off. Yield 63% (0.115 g), white powder, mp 244−245 °C. IR (ATR) 3021, 1662, 1634, 1602, 1488, 1329, 890, 762 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 7.29 (s, 2H, H-3, H-5), 7.75 (ddd, J = 8.0 Hz, J = 4.9 Hz, J = 0.7 Hz, 2H, H-5 Py), 8.61 (dt, J = 8.0 Hz, J = 1.9 Hz, 2H, H-4 Py), 8.94 (dd, J = 4.8 Hz, J = 1.9 Hz, 2H, H-6 Py), 9.39 (dd, J = 1.9 Hz, J = 0.7 Hz, 2H, H-2 Py); $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6): δ 117.5, 119.4, 124.6, 136.9, 148.7, 152.5, 154.2, 163.0, 174.9,

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176.9. Anal. Calcd for $C_{19}H_{10}N_6O_4$: C, 59.07; H, 2.61; N, 21.75. Found: C, 59.00; H, 2.71; N, 21.80.

2,6-Di(1*H*-tetrazol-5-yl)-4*H*-pyran-4-one (13). A solution of 2,6-dicyano-4*H*-pyran-4-one (**4**) (0.200 g, 1.369 mmol) in THF (6 mL) was added to a solution of NH_4Cl (0.220 g, 4.105 mmol) and NaN_3 (0.267 g, 4.105 mmol) in water (3 mL). The mixture was refluxed for 1.5 h (until phase separation disappeared). THF was evaporated, and the reaction mixture was treated with HCl (4 M). The precipitate that formed was filtered. Yield 87% (0.277 g), white crystals, decomp. >310 °C. IR (ATR) 3338, 3231, 3071, 3049, 1669, 1607, 1369, 946 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 6.99 (s, 2H, H-3, H-5), the NH protons were not found; $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 110.8, 155.6, 157.6, 178.6. Anal. Calcd for $C_7H_4N_8O_2 \cdot H_2O$: C, 33.61; H, 2.42; N, 44.79. Found: C, 33.82; H, 2.53; N, 44.64.

General Approach for the Preparation of 6-(3-Aryl-1,2,4-oxadiazol-5-yl)-4*H*-pyran-2-carbonitriles 15. A solution of triethylamine (0.322 g, 3.18 mmol) in Et_2O (2 mL) was cooled at −15 °C and added to a solution of substituted benzohydroxamic acid chloride **14** (3.28 mmol) in Et_2O (12 mL) cooled to −15 °C. The reaction mixture was stirred for 10 min at the same temperature, and the precipitate of triethylamine hydrochloride was filtered. The filtrate was added to a cooled to −10 °C solution of 2,6-dicyanopyrone **4** (0.400 g, 2.74 mmol) and $BF_3 \cdot Et_2O$ (0.466 g, 3.28 mmol) in Et_2O (14 mL) at −15 °C and was stirred for 1 h and, after that, at room temperature for 1 day. The precipitate was filtered off and heated in EtOH.

*4-Oxo-6-(3-phenyl-1,2,4-oxadiazol-5-yl)-4H-pyran-2-carbonitrile (**15a**).* Yield 65% (0.472 g), white powder, mp 210−211 °C. IR (ATR) 3054, 1653, 1389, 1359, 948, 745, 699 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.36 (d, J = 2.4 Hz, 1H, H-5), 7.49 (d, J = 2.4 Hz, 1H, H-3), 7.55−7.64 (m, 3H, H-3, H-4, H-5 Ph), 8.11 (dd, J = 8.3 Hz, J = 1.8 Hz, 2H, H-2, H-6 Ph); $^{13}C\{^1H\}$ (126 MHz, DMSO-d_6): δ 111.5, 118.9, 125.0, 125.6, 127.3, 129.5, 132.3, 137.8, 149.9, 168.2, 168.7, 175.8. Anal. Calcd for $C_{14}H_7N_3O_3$: C, 63.40; H, 2.66; N, 15.84. Found: C, 63.51; H, 2.67; N, 15.82.

*6-(3-(4-Bromophenyl)-1,2,4-oxadiazol-5-yl)-4-oxo-4H-pyran-2-carbonitrile (**15b**).* Yield 63% (0.594 g), yellow powder, mp 211−212 °C. IR (ATR) 3050, 1658, 1645, 1597, 1521, 1401, 1070, 910, 757 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.48 (d, J = 2.1 Hz, 1H, H-5), 7.63 (d, J = 2.1 Hz, 1H, H-3), 7.84 (d, J = 8.4 Hz, 2H, H-3, H-5 Ar), 8.04 (d, J = 8.4 Hz, 2H, H-2, H-6 Ar); ^{13}C NMR (126 MHz, DMSO-d_6): δ 111.5, 118.9, 124.2, 125.6, 126.0, 129.2, 132.6, 137.8, 149.8, 168.0, 168.4, 175.8. Calcd for $C_{14}H_6BrN_3O_3$: C, 48.86; H, 1.76; N, 12.21. Found: C, 48.70; H, 1.81; N, 12.11.

*6-(3-(4-Methoxyphenyl)-1,2,4-oxadiazol-5-yl)-4-oxo-4H-pyran-2-carbonitrile (**15c**).* Yield 29% (0.234 g), white powder, mp 215−216 °C. IR (ATR) 3054, 1663, 1648, 1608, 1370, 856 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 3.86 (s, 3H, CH_3), 7.16 (d, J = 8.3 Hz, 2H, H-2, H-6 Ar), 7.44 (d, J = 1.9 Hz, 1H, H-5), 7.62 (d, J = 1.9 Hz, 1H, H-3), 8.03 (d, J = 8.3 Hz, 2H, H-2, H-6 Ar); ^{13}C NMR (126 MHz, DMSO-d_6): δ 55.5, 111.6, 114.9, 117.2, 118.8, 125.5, 129.1, 137.8, 150.0, 162.3, 167.9, 168.4, 175.8. Anal. Calcd for $C_{15}H_9N_3O_4$: C, 61.02; H, 3.07; N, 14.23. Found: C, 60.74; H, 3.22; N, 14.04.

2-(5-(5-Phenyl-1,2,4-oxadiazol-3-yl)-1*H*-pyrazol-3-yl)-acetohydrazide (17). Cyanopyrone **15a** (0.100 g, 0.377 mmol) and hydrazine hydrate (0.200 g, 4.00 mmol) were stirred in EtOH (1 mL) at 0 °C for 1 h and then at 20 °C for 4 h. The solid that formed was filtered off and washed with EtOH. Yield 16% (0.107 g), white powder, mp 250−252 °C. IR (ATR) 3286, 3134, 2991, 1639, 1618, 1355, 753 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.54 (s, 2H, CH_2), 4.16 (br s, 2H, NH_2), 6.83 (s, 1H, CH Pz), 7.45−7.63 (m, 3H, Ph), 8.02−8.15 (m, 2H, Ph), 9.24 (s, 1H, NH), 12.80−14.20 (br s, 1H, NH Pz). ^{13}C NMR (101 MHz, DMSO-d_6) δ 30.6, 106.3, 126.2, 127.1, 129.3, 131.6, 136.9, 139.6, 167.1, 167.9, 171.5. Anal. Calcd for $C_{13}H_{12}N_6O_2 \cdot 0.33H_2O$: C, 53.80; H, 4.40; N, 28.96. Found: C, 54.04; H, 4.31; N, 28.88.

(*Z*)-*N*′-Hydroxy-4-oxo-6-(3-phenyl-1,2,4-oxadiazol-5-yl)-4*H*-pyran-2-carboximidamide (18). The solution of NH_2OH, which was obtained by stirring $NH_2OH \cdot HCl$ (0.150 g, 2.326 mmol) and KOH (0.130 g, 2.317 mmol) in MeOH (8 mL) for 5 min, was added to a suspension of 2-(3-phenyl-1,2,4-oxadiazol-5-yl)-6-cyano-4*H*-pyran-4-one (**15a**) (0.500 g, 1.885 mmol) in MeOH (6 mL) for 5 min in an ice bath. After that, the reaction mixture was refluxed for 2 h and left at room temperature for 1 day. The precipitate that formed was filtered off and washed with MeOH. Yield 91% (0.412 g), light yellow powder, mp 283−284 °C. IR (ATR) 3489, 3337, 2854, 1674, 1641, 1608, 1393, 1360, 951 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 5.86 (s, 2H, NH_2), 6.87 (d, J = 2.1 Hz, 1H, H-3), 7.19 (d, J = 2.1 Hz, 1H, H-5), 7.55−7.65 (m, 3H, H-3, H-4, H-5 Ph), 8.09 (dd, J = 7.5 Hz, J = 0.8 Hz, 2H, H-2, H-6, Ph), 10.67 (s, 1H, OH). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ 113.4, 117.7, 125.3, 127.2, 129.5, 132.2, 144.9, 149.1, 157.5, 168.6, 169.1, 177.3. Anal. Calcd for $C_{14}H_{10}N_4O_4 \cdot 0.33H_2O$: C, 56.38; H, 3.82; N, 18.78. Found: C, 56.06; H, 3.46; N, 18.49.

2-(3-Phenyl-1,2,4-oxadiazol-5-yl)-6-(1*H*-tetrazol-5-yl)-4*H*-pyran-4-one (19a). 2-(3-Phenyl-1,2,4-oxadiazol-5-yl)-6-cyano-4*H*-pyran-4-one (**15a**) (0.100 g, 0.377 mmol) was added to a solution of NH_4Cl (0.040 g, 0.748 mmol) and NaN_3 (0.050 g, 0.769 mmol) in H_2O (2 mL) and THF (4 mL). The reaction mixture was refluxed for 1 h (until the phase separation disappeared), and then THF was evaporated. The resulted solution was cooled to room temperature and treated with concd HCl. The precipitate that formed was filtered and washed with water. Yield 98% (0.114 g), white powder, mp 290−291 °C. IR (ATR): 3062, 1661, 1616, 1442, 1351, 944, 748, 701 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.23 (d, J = 2.4 Hz, 1H, H-5), 7.34 (d, J = 2.4 Hz, 1H, H-3), 7.54−7.64 (m, 3H, H-3, H-4, H-5 Ph), 8.12 (d, J = 8.1 Hz, J = 1.3 Hz, 2 H, H-2, H-6 Ph), the NH proton was not observed. ^{13}C NMR (126 MHz, DMSO-d_6): δ 115.8, 118.3, 125.1, 127.2, 129.3, 132.1, 149.3, 153.0, 153.5, 168.6, 168.7, 176.6. Anal. Calcd for $C_{14}H_8N_6O_3 \cdot 0.67H_2O$: C, 52.49; H, 2.94; N, 26.24. Found: C, 52.73; H, 3.13; N, 25.97.

2-(3-(4-Bromophenyl)-1,2,4-oxadiazol-5-yl)-6-(1*H*-tetrazol-5-yl)-4*H*-pyran-4-one (19b). 2-(3-(4-Bromophenyl)-1,2,4-oxadiazol-5-yl)-6-cyano-4*H*-pyran-4-one **15b** (0.260 g, 0.768 mmol) was added to a solution of $NHEt_2 \cdot HCl$ (0.168 g, 1.534 mmol) and NaN_3 (0.100 g, 1.535 mmol) in H_2O (3 mL) and THF (6 mL). The reaction mixture was refluxed for 12 h. The resulted solution was cooled to room temperature and treated with concd HCl. The precipitate that formed was filtered and washed with water. Yield 93% (0.315 g), orange powder, 245−250 °C. IR (ATR): 3051, 1660, 1617, 1350, 945, 703 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.23 (d, J = 2.4 Hz, 1H, H-5), 7.40 (d, J = 2.4 Hz, 1H, H-3), 7.85 (d, J = 8.5 Hz, 2H, H-3, H-5 Ar), 8.04 (d, J = 8.5 Hz, 2H, H-2, H-6 Ar), the NH proton was not found; ^{13}C NMR (126 MHz, DMSO-

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d_6): δ 115.7, 118.4, 124.4, 125.9, 129.2, 132.6, 149.3, 153.2, 153.6, 168.0, 169.0, 176.7. Anal. Calcd for $C_{14}H_7BrN_6O_3$: C, 43.43; H, 1.82; N, 21.71. Found: C, 43.59; H, 1.71; N, 21.62.

2-(3-Phenyl-1,2,4-oxadiazol-5-yl)-6-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)-4*H*-pyran-4-one (20a). A solution of $(CF_3CO)_2O$ (0.210 g, 0.999 mmol) in CH_2Cl_2 (3 mL) was added dropwise to amidoxime **18** (0.107 g, 0.359 mmol) and pyridine (0.080 g, 1.011 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was refluxed for 1 h; after that, CH_2Cl_2 was evaporated, the residue was treated with H_2O, and the precipitate that formed was filtered. The product was recrystallized from toluene−hexane (1:10). Yield 81% (0.135 g), white powder, mp 176−177 °C. IR (ATR) 3052, 1661, 1637, 1177, 945, 902, 755 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.25 (d, J = 2.4 Hz, 1H, H-5), 7.41 (d, J = 2.4 Hz, 1H, H-3), 7.61 (m, 3H, H-3, H-4, H-5 Ph), 8.11 (m, 2H, H-2, H-6 Ph); ^{19}F NMR (377 MHz, DMSO-d_6) δ 100.20 (s, 3F, CF_3); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 115.3 (q, J = 273.7 Hz, CF_3), 118.3, 118.5, 125.1, 127.2, 129.3, 132.1, 149.5, 150.9, 162.9, 165.8 (q, J = 44.6 Hz, CF_3), 168.5, 168.6, 176.3. Anal. Calcd for $C_{16}H_7F_3N_4O_4$: C, 51.08; H, 1.88; N, 14.89. Found: C, 51.05; H, 1.55; N, 14.86.

2-(5-Phenyl-1,2,4-oxadiazol-3-yl)-6-(3-phenyl-1,2,4-oxadiazol-5-yl)-4*H*-pyran-4-one (20b). Benzoyl chloride (0.094 g, 0.669 mmol) was added dropwise to 2-amidoxime-6-(3-phenyl-1,2,4-oxadiazol-5-yl)-4*H*-pyran-4-one (**18**) (0.100 g, 0.335 mmol) and pyridine (0.053 g, 0.670 mmol) in DMF (2 mL). The reaction mixture was heated at 120 °C for 5 h and was kept at room temperature for 1 day. The precipitate that formed was filtered off and washed with EtOH. Yield 44% (0.056 g), white powder, mp 233−234 °C. IR (ATR): 3060, 1660, 1636, 1351, 947, 748 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.27 (d, J = 2.4 Hz, 1H, H-3), 7.40 (d, J = 2.4 Hz, 1H, H-5), 7.67 (m, 6H, Ph), 8.17 (m, 4H, Ph); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 117.4, 118.3, 122.4, 125.0, 127.0, 128.0, 129.1, 129.4, 131.9, 133.7, 149.3, 152.4, 162.7, 168.46, 168.54, 176.3 (1C was not observed). Anal. Calcd for $C_{21}H_{12}N_4O_4$: C, 65.62; H, 3.15; N, 14.58. Found: C, 65.44; H, 3.16; N, 14.60.

General Approach for the Synthesis of Bis(azolyl)-pyrones 21. The corresponding pyrone **19** (0.75 mmol) was refluxed in Ac_2O (6 mL) for 8 h. The solvent was evaporated in an evaporating dish at room temperature. The precipitate that formed was washed with EtOH.

*2-(5-Methyl-1,3,4-oxadiazol-2-yl)-6-(3-phenyl-1,2,4-oxadiazol-5-yl)-4H-pyran-4-one (**21a**).* Yield 77% (0.217 g), gray powder, 188−190 °C. IR (ATR): 3041, 1656, 1623, 1567, 1367, 944, 747 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.69 (s, 3H, Me), 7.23 (d, J = 2.4 Hz, 1H, H-3), 7.44 (d, J = 2.4 Hz, 1H, H-5), 7.59−7.72 (3H, m, Ph), 8.12 (dd, J = 8.3 Hz, J = 1.2 Hz, 2H, H-2, H-6 Ph); $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ 10.7, 116.4, 118.5, 125.1, 127.3, 129.5, 132.2, 149.3, 149.6, 157.7, 166.1, 168.6, 168.7, 176.2. Anal. Calcd for $C_{16}H_{10}N_4O_4 \cdot 0.67EtOH$: C, 58.62; H, 3.86; N, 16.09. Found: C, 58.62; H, 3.56; N, 16.15.

*2-(3-(4-Bromophenyl)-1,2,4-oxadiazol-5-yl)-6-(5-methyl-1,3,4-oxadiazol-2-yl)-4H-pyran-4-one (**21b**).* Yield 72% (0.217 g), gray powder, mp 233−235 °C. IR (ATR) 3060, 1668, 1645, 1544, 1404, 1339, 943, 754 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.68 (s, 3H, Me), 7.23 (d, J = 2.5 Hz, 1H, H-3), 7.45 (d, J = 2.5 Hz, 1H, H-5), 7.86 (d, J = 8.5 Hz, 2H, H-3, H-5 Ar), 8.05 (d, J = 8.5 Hz, 2H, H-2, H-6 Ar); $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6): δ 10.6, 116.4, 118.5, 124.3, 125.8, 129.1, 132.5, 149.2, 149.5, 157.6, 166.0, 168.0, 168.7, 176.4. Anal. Calcd for $C_{16}H_9BrN_4O_4$: C, 47.90; H, 2.26; N, 13.97. Found: C, 47.61; H, 2.29; N, 13.75.

2,6-Bis(5-methyl-1,3,4-oxadiazol-2-yl)-4*H*-pyran-4-one (22a). 2,6-Di(1*H*-tetrazol-5-yl)-4*H*-pyran-4-one (**12**) (0.100 g, 0.43 mmol) was refluxed in Ac_2O (10 mL) for 48 h. The solvent was evaporated in an evaporating dish at room temperature. The solid that formed was washed with EtOH. Yield 92% (0.103 g), brown crystals, mp 314−316 °C. IR (ATR): 3060, 3039, 1662, 1640, 1570, 1528, 1421, 1331, 1116, 1035, 897, 734 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.67 (s, 6H, 2Me), 7.16 (s, 2H, H-3, H-5); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 10.7, 116.2, 149.4, 157.7, 166.0, 176.5. Anal. Calcd for $C_{11}H_8N_4O_4$: C, 50.77; H, 3.10; N, 21.53. Found: C, 50.80; H, 2.89; N, 21.25.

2,6-Bis(5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)-4*H*-pyran-4-one (22b). 2,6-Bis(tetrazolyl)-4-pyrones (**13**) (0.020 g, 0.086 mmol) were stirred in trifluoracetic acid anhydride (1 mL) at room temperature for 10 days (until complete dissolution) in a closed flask. Since trifluoracetic acid anhydride is volatile and N_2 forms during the transformation, the reaction flask should be able to withstand pressure. The excess of trifluoracetic acid anhydride was evaporated, and CH_2Cl_2 (4 mL) and H_2O (4 mL) were added. The organic phase was separated, dried with Na_2SO_4, and evaporated. The solid was recrystallized from a mixture of toluene−hexane (1:10). Yield 44% (0.014 g), yellow powder, decomp. 200 °C. IR (ATR): 3078, 1668, 1623, 1642, 1637, 1536, 1385, 1117, 942 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.48 (s, 2H, H-3, H-5); ^{19}F NMR (376 MHz, DMSO-d_6) δ 98.42 (s, 6F, $2CF_3$); $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ 118.3, 148.5, 114.8 (q, J = 271.8 Hz, CF_3), 155.0 (q, J = 44.7 Hz, C-CF_3), 159.4, 176.0. Anal. Calcd for $C_{11}H_2F_6N_4O_4$: C, 35.89; H, 0.55; N, 15.22. Found: C, 35.71; H, 0.66; N, 15.22.

General Method for the Preparation of 2,6-Bis(5-aryl-1,3,4-oxadiazol-2-yl)-4*H*-pyran-4-ones 22c and 22d. 2,6-Di(1*H*-tetrazol-5-yl)-4*H*-pyran-4-one (**13**) (0.100 g, 0.431 mmol) was heated in neat aroyl chloride (1 mL) for 8 h at 170 °C. The reaction mixture was cooled to room temperature, EtOH was added, and the precipitate was filtered and washed with EtOH.

*2,6-Bis(5-phenyl-1,3,4-oxadiazol-2-yl)-4H-pyran-4-one (**22c**).* Yield 60% (0.099 g), brown powder, mp 232−233 °C. IR (ATR) 3064, 1660, 1642, 1522, 1418, 1258, 1073, 941, 784 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 7.49 (s, 2H, H-3, H-5), 7.66−7.75 (m, 6H, Ph), 8.21 (d, J = 8.5 Hz, 4H, H-2, H-6 Ph); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 116.8, 122.4, 127.2, 129.6, 132.9, 149.4, 157.7, 165.3, 176.7. Anal. Calcd for $C_{21}H_{12}N_4O_4$: C, 65.63; H, 3.15; N, 14.58. Found: C, 65.71; H, 2.96; N, 14.23.

*2,6-Bis(5-(furan-2-yl)-1,3,4-oxadiazol-2-yl)-4H-pyran-4-one (**22d**).* Yield 44% (0.070 g), brown powder, mp 248−249 °C. IR (ATR): 3122, 1660, 1627, 1575, 1516, 1099, 937, 752 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 6.89 (dd, J = 3.3 Hz, J = 1.3 Hz, 2H, H-4 furan), 7.32 (s, 2H, H-3, H-5), 7.61 (d, J = 3.3 Hz, 2H, H-3 furan), 8.18 (d, J = 1.3 Hz, 2H, H-5 furan); $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ 113.1, 116.7, 137.9, 148.1, 149.3, 157.0, 158.0, 176.5 (1C was not observed). Anal. Calcd for $C_7H_3N_9O$: C, 36.37; H, 2.18; N, 54.53. Found: C, 36.21; H, 2.23; N, 54.42. HRMS (ESI/Q-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_9N_4O_6$ 365.0522, found 365.0531.

2,6-Di(1*H*-tetrazol-5-yl)pyridin-4-ol (23a). 2,6-Bis-(tetrazol-5-yl)-4*H*-pyran-4-one **13** (0.100 g, 0.431 mmol) was

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added in aqueous ammonia solution (25%, 2 mL). The mixture was stirred for 48 h at room temperature in a closed flask, which is able to withstand pressure. The reaction mixture was diluted with HCl (4 M), and the resulting precipitate was filtered off. Yield 84% (0.084 g), decomp. 310 °C. IR (ATR): 3222, 3044, 2946, 1616, 1564, 1281, 1086, 991, 893 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.64 (s, 2H, H-3, H-5), the NH and OH protons were not observed; $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 111.5, 145.6, 154.9, 166.5. Anal. Calcd for $C_7H_5N_9O$: C, 36.37; H, 2.18; N, 54.53. Found: C, 36.21; H, 2.23; N, 54.42.

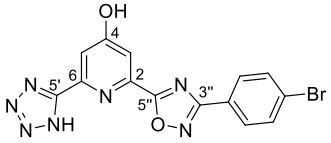
General Method for the Preparation of Pyridinols 23b−23g. The corresponding pyrone (0.143 mmol) was heated in a solution of NH_3 in EtOH (3 mL, 12−15%) in an autoclave (25 mL) at 100 °C for 5 h. Then cooling overnight, the resulting precipitate was filtered off, washed with EtOH, and dried at 120 °C. For **23g**, the filtrate was evaporated, and the product was separated and washed with minimal volume of EtOH.

*2,6-Bis(5-phenyl-1,2,4-oxadiazol-3-yl)pyridin-4-ol (**23b**).* From pyrone **11c**. Yield 83% (0.046 g), brown crystals, mp 264−265 °C. IR (ATR): 3368, 3068, 1640, 1609, 1557, 1448, 1373, 1128, 867, 793 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.67 (s, 2H, H-3, H-5), 7.69 (dd, J = 7.8 Hz, J = 7.4 Hz, 4H, H-3, H-5 Ph), 7.77 (tt, J = 7.4 Hz, J = 1.2 Hz, 2H, H-4 Ph), 8.24 (dd, J = 7.8 Hz, J = 1.2 Hz, 4H, H-2, H-6 Ph), the OH proton was not observed; $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 114.8, 123.5, 127.9, 129.5, 133.2, 147.4, 168.8, 170.2, 175.4. HRMS (ESI/Q-TOF) m/z $[M + H]^+$ calcd for $C_{21}H_{14}N_5O_3$ 383.1097, found 384.1107.

*2,6-Bis(5-(pyridin-3-yl)-1,2,4-oxadiazol-3-yl)pyridin-4-ol (**23c**).* From pyrone **11e**. Yield 87% (0.048 g), beige powder, mp 325−327 °C. IR (ATR): 3179, 3066, 2793, 1607, 1560, 1510, 1411, 1341, 972, 793 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.73 (ddd, J = 7.9 Hz, J = 4.9 Hz, J = 0.7 Hz, 2H, H-5 Py), 7.77 (s, 2H, H-3, H-5), 8.61 (dt, J = 8.1 Hz, J = 1.6 Hz, 2H, H-4 Py), 8.92 (dd, J = 4.9 Hz, J = 1.6 Hz, 2H, H-6 Py), 9.39 (dd, J = 2.3 Hz, J = 0.7 Hz, 2H, H-2 Py), 11.61 (s, 1H, NH); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 115.6, 120.1, 124.4, 135.6, 146.9, 148.5, 153.6, 168.9, 171.6, 173.7. Anal. Calcd for $C_{19}H_{11}N_7O_3$: C, 59.22; H, 2.88; N, 25.44. Found: C, 59.41; H, 2.89; N, 25.60.

*2-(5-Phenyl-1,2,4-oxadiazol-3-yl)-6-(3-phenyl-1,2,4-oxadiazol-5-yl)pyridin-4-ol (**23d**).* From pyrone **20b**. Yield 85% (0.047 g), yellow powder, mp 295−296 °C. IR (ATR): 3090, 1635, 1616, 1356, 1211, 981 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ 7.60−7.66 (m, 3H, Ph), 7.68 (d, J = 1.9 Hz, CH pyridine), 7.69 (t, J = 7.6 Hz, 2H, H-3, H-5 Ph), 7.74 (d, J = 1.9 Hz, CH pyridine), 7.76 (t, J = 7.5 Hz, H-4 Ph), 8.14 (d, J = 7.6 Hz, J = 1.4 Hz, 2H, H-2, H-6 Ph), 8.23 (d, J = 7.5 Hz, 2H, H-2, H-6 Ph), the OH proton was not observed; $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6): δ 114.9, 115.2, 123.3, 126.0, 127.1, 127.9, 129.2, 129.5, 131.6, 133.3, 144.5, 147.6, 168.2, 168.3, 169.0, 174.6, 175.6. HRMS (ESI/Q-TOF) m/z $[M + H]^+$ calcd for $C_{21}H_{14}N_5O_3$ 384.1097, found 384.1107.

*2-(3-(4-Bromophenyl)-1,2,4-oxadiazol-5-yl)-6-(2H-tetrazol-5-yl)pyridin-4-ol (**23e**).* From pyrone **19b**. Yield 63% (0.035 g), beige powder, mp 255−256 °C. IR (ATR): 3261, 2671, 1615, 1578, 1561, 1518, 1404, 1252, 966, 769 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 7.00−7.50 (br s, 1H, NH), 7.61 (d, J = 2.3 Hz, 1H, H-5), 7.72 (d, J = 2.3 Hz, 1H, H-3), 7.83 (d, J = 8.6 Hz, 2H, H-3, H-5 Ar), 8.08 (d, J = 8.6 Hz, 2H, H-2, H-6 Ar), the OH proton was not observed; ^{13}C NMR (101 MHz, DMSO-d_6): δ 111.2, 111.6, 125.28, 125.31, 129.1, 132.4, 143.7 (C-5″), 153.6 (C-5′), 160.7 (C-6), 165.4 (C-4), 167.5 (C-3″), 175.1 (C-2). HRMS (ESI/Q-TOF) m/z $[M + H]^+$ calcd for $C_{14}H_9N_7O_2Br$ 386.0001, found 386.0028.



*2-(3-(4-Bromophenyl)-1,2,4-oxadiazol-5-yl)-6-(5-methyl-1,3,4-oxadiazol-2-yl)pyridin-4-ol (**23f**).* From pyrone **21b**. Yield 76% (0.044 g), beige powder, mp 315−316 °C. IR (ATR): 3193, 3047, 2954, 1610, 1557, 1407, 1124, 987, 831 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 2.66 (s, 3H, Me), 7.66 (d, J = 2.2 Hz, 1H, CH pyridine), 7.75 (d, J = 2.2 Hz, 1H, CH pyridine), 7.82 (d, J = 8.6 Hz, 2H, H-3, H-5 Ar), 8.05 (d, J = 8.6 Hz, 2H, H-2, H-6 Ar), the OH proton was not observed. $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 10.7, 116.1, 117.4, 125.1, 125.5, 129.1, 132.3, 143.7, 144.3, 164.2, 164.4, 167.5, 173.3, 175.7. HRMS (ESI/Q-TOF) m/z $[M + H]^+$ calcd for $C_{16}H_{11}N_5O_3Br$ 400.0045, found 400.0054.

*2,6-Bis(5-methyl-1,3,4-oxadiazol-2-yl)pyridin-4-ol (**23g**).* From pyrone **22a**. Yield 66% (0.025 g), yellow powder, mp 312−314 °C. IR (ATR): 3395, 1662, 1616, 1549, 1429, 1236, 986, 865 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.61 (s, 6H, 2Me), 7.36 (s, 2H, H-3, H-5), the OH proton was not observed. $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ 10.7, 114.0, 144.3, 163.9, 164.6, 170.9. HRMS (ESI/Q-TOF) m/z $[M + H]^+$ calcd for $C_{11}H_{10}N_5O_3$ 260.0784, found 260.0795.

X-ray Diffraction Study of Compound 22a. Intensity data for compound **22a** were collected on an "Xcalibur E" diffractometer at 295(2) (Mo Kα radiation, graphite monochromator, ω-scan, radiation wavelength = 0.7107). The structures were solved by direct methods and refined by the full-matrix least-squares method using the SHELX97 program package.[30] All non-hydrogen atoms were refined with anisotropic atomic displacement, and hydrogen atoms were included at the calculated positions using a riding model. The geometrical parameters and the figures were analyzed using the program OLEX2.[31] Crystal data for **22a** ($C_{11}H_8N_4O_4$, 260.21). Monoclinic crystal, space group P 21/c, a = 11.4140(14) Å, b = 10.9106(9) Å, c = 9.0833(11) Å, α = 90.00, β = 100.360(12), γ = 90.00, V = 1112.7(2) $Å^3$, Dc = 1.553 g cm^{-3}, absorption coefficient μ = 0.122 mm^{-1}, Z = 4. The intensities of 2882 independent reflections (R_{int} = 0.0659) were measured. The final discrepancy factors R_1 = 0.0704, wR_2 = 0.1705, GooF = 1.047 for 1442 reflections with $I > 2\sigma(I)$; R_1 = 0.1361, wR_2 = 0.2384 (all data). Largest different peaks and holes: 0.27 and −0.34 e $Å^{-3}$. Completeness to θ = 26.00° (99.4%). Deposition number CCDC 2022244.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c05357.

Optimization of the reaction conditions for the cyclization of triketone **1** to ester **2** and ^1H and 13C NMR spectra (PDF)

X-ray crystallographic data of **22a** (CIF)

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Notes

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